

REMARKS

Claims 1-17 and 19-29 are currently pending. Claim 18 was previously cancelled. Claims 1, 3, 5-17, and 19-29 are currently withdrawn as being directed to non-elected subject matter. Claims 30-33 are newly added. Claims 2, 4-7, and 30-33 are currently subject to examination. Claims 2, 5, and 6 are amended herein.

Claim 2 is amended herein to recite a transcription factor decoy comprising a concatemerized double-stranded oligonucleotide molecule, wherein the concatemerized double-stranded oligonucleotide molecule comprises at least 10 end-to-end repeated copies of a domain, wherein each of said domains comprises a nucleotide sequence that acts as a transcription factor decoy for a transcription factor, and wherein each of said domains comprises from about 10 to about 40 nucleotide base pairs. Support for this amendment is found, for example, at paragraphs [00398], [00415], and [00418] of the Specification as originally filed.

Claim 5 is amended herein to refer to the antecedent term "transcription factor decoy."

Claim 6 is amended herein to refer to the antecedent term "domain."

New claim 30 recites the transcription factor decoy of claim 2, wherein each domain comprises from about 14 to about 40 nucleotide base pairs. Support for this amendment is found, for example, at paragraph [00415] of the Specification as originally filed.

New claim 31 recites the transcription factor decoy of claim 2, wherein each domain comprises from about 12 to about 25 nucleotide base pairs. Support for this amendment is found, for example, at paragraph [00415] of the Specification as originally filed.

New claim 32 recites the transcription factor decoy of claim 2, wherein the concatemerized double-stranded oligonucleotide molecule comprises at least 15 end-to-end repeated copies of domain. Support for this amendment is found, for example, at paragraph [00363] of the Specification as originally filed.

New claim 33 recites the transcription factor decoy of claim 2, wherein the concatemerized double-stranded oligonucleotide molecule comprises at least 20 end-to-end repeated copies of a domain. Support for this amendment is found, for example, at paragraph [00363] of the Specification as originally filed.

It is believed that no new matter has been added. As dependent claim 18 was previously cancelled, the claims fee for 3 additional dependent claims is submitted with this filing. Entry of the present Amendment is believed to be in order and is respectfully requested.

Claim Rejection - 35 U.S.C. §102

Claims 2 and 4-7 are rejected under 35 .S.C. §102(a) and (e) as being anticipated by Dzau et al., U.S. Application No. 2003/0186922, published October 2, 2003, filed April 25, 2003, priority date October 29, 1993 (hereafter, "Dzau"). Specifically, the Examiner asserted:

With regard to the limitation of claims 2 and 5, Dzau et al. teach oligodeoxynucleotide decoys for the prophylactic or therapeutic treatment of diseases associated with the binding of endogenous transcription factors to genes involved in cell growth, differentiation and signaling or to viral genes. By inhibiting endogenous trans-activating factors from binding transcription regulatory regions, the decoys modulate gene expression and thereby regulating pathological processes including inflammation, intimal hyperplasia, angiogenesis, neoplasia, immune responses and viral infection.

Dzau et al. teaches [a] double-stranded DNA molecule comprising complementary decoy oligonucleotides containing two E2F transcription factor binding sites...

With regard to the limitation of claim 4, Dzau et al. teaches the decoys may comprise a portion of a larger plasmid, including viral vectors, capable of episomal maintenance or constitutive replication in the target cell to provide longer term or enhanced intracellular exposure to the decoy sequence. Plasmids comprising [a] promoter that regulates the expresse[d] transcription factor decoy of interest are selected based on compatibility with the target cell (i.e. tissue specificity), size and restriction sites, replicative frequency, copy number maintenance, etc. For example, plasmids with relatively short half-lives in the target cell are preferred in situations where it is desirable to maintain therapeutic transcriptional modulation for less than the lifetime of the target cell.

With regard to the limitation of claims 6 and 7, Dzau et al. teaches dsDNA is characterized by having a sequence specific for binding to a transcription

factor, wherein said transcription product of said gene is necessary for cell proliferation, herein said transcription factor is E2F, AP-1, or NF-kB.

Thus, Dzau et al. clearly anticipates claims 2 and 4-7 of [the] instant application.

Applicant traverses the rejection and requests reconsideration.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicant submits Dzau fails to teach or suggest all elements of the presently claimed invention. Claim 2, as presently amended, recites a transcription factor decoy comprising a concatemered double-stranded oligonucleotide molecule, wherein the concatemered double-stranded oligonucleotide molecule comprises at least 10 end-to-end repeated copies of a domain, wherein each of said domains comprises a nucleotide sequence that acts as a transcription factor decoy for a transcription factor, and wherein each of said domains comprises from about 10 to about 40 nucleotide base pairs. Applicant finds no teaching or suggestion in Dzau of a transcription factor decoy comprising at least 10 end-to-end repeated copies of a domain, each domain comprising from about 10 to about 40 nucleotide base pairs. Although Dzau discloses the decoys of his invention may be constructed with serial repetitions of the binding sequences, Dzau is limited to comparatively short oligonucleotides "having fewer than 100 bp, and usually fewer than 50 bp." See paragraph [0021] of Dzau, emphasis added. The longest oligonucleotide disclosed in Dzau's working examples is a 30 bp oligonucleotide decoy having two 8 bp E2F cis elements. See paragraphs [0034]-[0038] of Dzau. Conversely, the instantly claimed transcription factor decoys are comparatively longer and comprise at least 10 repeated copies of a domain, each domain comprising about 10 to about 40 nucleotide bases.

These longer concatemers confer significant benefits over the shorter oligonucleotides of Dzau, as disclosed in paragraphs [00034] and [00406] of the Specification as filed. Dzau teaches

that in order to increase intracellular exposure to a decoy, the decoy must be placed in a plasmid capable of episomal maintenance or replication (see paragraph [0021] of Dzau); such is not the case with the longer oligonucleotides of the instant claims. The concatemers recited in claim 2 degrade more slowly in cells, thus increasing the half-life of the nucleotide within the cell and allowing for less frequent administration of the decoy to achieve a desired effect. Concatemers of the present invention increase the efficiency of each single decoy molecule, since each molecule contains multiple (at least 10) copies of a domain that acts as a transcription factor decoy. Further, the use of longer concatemers of multiple binding sites allows the decoy to bind more transcription factors per molecule, allowing the delivery of more decoy with the use of less delivery vehicle, which may reduce the side effects of delivery vehicles such as polymers or viral vectors. See paragraphs [00034] and [00406] of the Specification as filed. Dzau neither suggests nor predicts the benefits of the concatemers according to instant claim 2.

Hence, Applicant submits base claim 2 is not anticipated by Dzau. Since claims 4-7 depend from claim 2 and necessarily include all the limitations of the base claim, Applicant submits claims 4-7 are also not anticipated by Dzau. Reconsideration and a withdrawal of the rejection of claims 2 and 4-7 under 35 U.S.C. §102(a) or (e) as being anticipated by Dzau is therefore respectfully requested.

Claims 2, 4, 5, and 7 are rejected under 35 U.S.C. §102(b) as being anticipated by Weintraub et al., *Retinoblastoma protein switches the E2F site from positive to negative element*, Nature 358(6383): 259-61 (1992) (hereafter, "Weintraub"). Specifically, the Examiner asserted:

With regard to the limitation of transcription factor decoy recited in claim 2 and the limitation regarding gene expression associated with pathogenesis recited in claim 5, Weintraub et al. teaches that originally E2F sites were identified as elements in the promoters of adenovirus early genes that are necessary for activation of these genes by the early protein E1a. E2F promoter elements have been shown to be important for transcriptional activation of several

genes critical for progression through the cell cycle. Weintraub teaches that during the G1 phase of the cell cycle, the E2F protein forms a complex with the cell-cycle protein Rb (retinoblastoma) and it has been suggested that this binding of Rb to E2F inactivates E2F. Weintraub et al. shows that Rb-E2F is an active complex that, when bound to the E2F site, inhibits the activity of other promoter elements and thus silences transcription. Weintraub et al. proposes that the ability of this complex to inhibit transcription is integral to the function of Rb and provide evidence that E2F is a positive element in the absence of an active form of Rb (only the under-phosphorylated form binds) and that the phosphorylation state of Rb changes during progression through the cell cycle. Weintraub et al. suggest that the E2F site alternates between a positive and negative element with the phosphorylation/dephosphorylation cycle of Rb, and this cyclic activity may be responsible for activating and then inhibiting genes during the cell cycle.

With regard to the characteristics regarding transcription factor decoy recited in claims 2, 4, 5, and 7, Weintraub et al. teaches that the role of the E2F protein in E1a promoter activity was examined in transfection assays in which a competitor plasmid containing E2F binding sites was cotransfected with the plasmid pE1aCAT, which contains the E1a promoter fused to the gene for chloramphenicol acetyltransferase (CAT). This competitive[ly] binds and sequesters E2F, thus preventing it from interacting with the E1a promoter...

It is noted that there are multiple end-to-end E2F sites present in the promoter of double-stranded plasmid pTA-ATF-E2F-CAT and plasmid pSV-E2F-CAT. Furthermore, the AP-1 site and ATF site present in the plasmids taught by Weintraub et al. are the binding sites of transcription factors AP-1, ATF2 and ATF3 recited in claim 7 of the instant application.

Thus, Weintraub et al. clearly anticipates claims 2, 4, 5, and 7 of [the] instant application.

Applicant traverses the rejection and requests reconsideration.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicant submits Weintraub fails to teach or suggest all elements of the presently claimed invention. Claim 2, as presently amended, recites a transcription factor decoy comprising a concatemerized double-stranded oligonucleotide molecule, wherein the concatemerized double-stranded oligonucleotide molecule comprises at least 10 end-to-end repeated copies of a domain, wherein each of said domains comprises a nucleotide sequence that acts as a transcription factor decoy for a transcription factor, and wherein each of said domains comprises from about 10 to

about 40 nucleotide base pairs. Applicant finds no teaching or suggestion in Weintraub of a transcription factor decoy comprising at least 10 end-to-end repeated copies of a domain that acts as a transcription factor decoy, each domain comprising from about 10 to about 40 nucleotide base pairs. Rather, Weintraub is limited to comparatively short constructs (see figure 2a of Weintraub). At most, Weintraub discloses a construct having only three domains comprised of two E2F sites and either one ATF or one AP-1 site. Conversely, the instantly claimed transcription factor decoys are comparatively longer and comprise at least 10 end-to-end repeated copies of a domain, each domain comprising about 10 to about 40 nucleotide base pairs.

As noted in detail above, the longer concatemers of the instant claims confer significant benefits over shorter oligonucleotides, such as those disclosed by Weintraub. The concatemers recited in claim 2 degrade more slowly in cells, thus increasing the half-life of the nucleotide within the cell and allowing for less frequent administration of the decoy to achieve a desired effect. Concatemers of the present invention increase the efficiency of each single decoy molecule, since each molecule contains multiple (at least 10) copies of a domain that acts as a transcription factor decoy. Further, the use of longer concatemers of multiple binding sites allows the decoy to bind more transcription factors per molecule, allowing the delivery of more decoy with the use of less delivery vehicle, which may reduce the side effects of delivery vehicles such as polymers or viral vectors. See paragraphs [00034] and [00406] of the Specification as filed. Weintraub neither suggests nor predicts the benefits of the concatemers according to instant claim 2.

Hence, Applicant submits base claim 2 is not anticipated by Weintraub. Since claims 4, 5, and 7 depend from claim 2 and necessarily include all the limitations of the base claim, Applicant submits claims 4, 5, and 7 are also not anticipated by Weintraub. Applicant

respectfully requests reconsideration and a withdrawal of the rejection of claims 2, 4, 5, and 7 under 35 U.S.C. §102(b) as being anticipated by Weintraub.

Claim Rejection - 35 U.S.C §103(a)

Claims 2 and 6 are rejected under 35 U.S.C. §103(a) as being unpatentable over Weintraub in view of Sharma et al., *Transcription factor decoy approach to decipher the role of NF-kappaB oncogenesis*, Anticancer Research 16(1): 61-69 (1996) (hereafter, "Sharma"). Specifically, the Examiner reiterates the assertions as to the teachings of Weintraub with respect to claims 2, 4, 5, and 7 above, and then notes that Weintraub does not explicitly teach the limitation "wherein the decoys are NF-kB-specific" recited in claim 6 of the instant application. The Examiner applies Sharma as follows:

At the time the claimed invention was made, [transcription] factor decoy for NF-kappaB transcription factor were known in the art. For instance, Sharma et al. teaches transcription factor decoy approach to decipher the role of NF-kappaB in oncogenesis. In an effort to decipher the role of homo- vs. heterodimeric NF-kappaB in regulating tumor cell growth, Sharma et al. used a decoy approach to trap these complexes in vivo. Using double-stranded phosphorothioates as a direct in vivo competitor for homo- vs. heterodimeric NF-kappa B, Sharma et al demonstrate that decoys more specific to RelA inhibit [] tumor cell growth in vitro. Sharma et al. demonstrate that RelA, either as a homodimer or a heterodimer with some other members of the Rel family and not the classical NF-kB (RelA/NK-kB), is involved in the differential growth control of tumor cells.

Therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Weintraub et al. regarding transcription factor decoy comprising a concatenated double-stranded oligonucleotide molecule comprising at least two end-to-end repeated copies of a nucleotide sequence comprising a sequence or sequences that act as transcription factor decoys, with the teachings of Sharma et al., regarding transcription factor decoy approach to decipher the role of NF-kB transcription factor in oncogenesis, to arrive at claimed methods recited in claim 6 of [the] instant application, by replacing E2F transcription factor binding sites taught by Weintraub with NF-kB transcription factor binding sites taught by Sharma et al.

One having an ordinary skill in the art would have been motivated to combine the teachings of Weintraub et al. with the teachings of Sharma et al. because Sharma et al. specifically teach a functional role of NF-kB transcription factor in regulation of oncogenesis whereas Weintraub et al. teaches

retinoblastoma (RB) protein regulating E2F transcription factor binding to E2F sites.

There would have been a reasonable expectation of success given (i) the successful demonstration of plasmids with multiple E2F transcription factor binding sites functioning as a transcription factor decoy that sequesters E2F transcription factor and thus preventing E2F transcription factor from interacting with the E1a promoter, by the teachings of Weintraub et al., and (ii) the successful demonstration of transcription factor decoy approach to decipher the role of homo- vs. heterodimeric NF-kB in regulating tumor cell growth, by the teachings of Sharma et al.

Applicant traverses the rejection and requests reconsideration.

As noted above in detail, Applicant submits Weintraub fails to teach or suggest each element of instant base claim 2. Namely, Applicant finds no teaching or suggestion of a concatemericized double-stranded oligonucleotide molecule comprising at least 10 end-to-end repeated copies of a domain, wherein each domain comprises from about 10 to about 40 nucleotide base pairs. Applicant finds no teaching or suggestion in Sharma that overcomes this deficiency, such that Weintraub and Sharma, either alone or in combination, teach all elements of instant claim 2.

Accordingly, Applicant submits the rejection of claim 2 under 35 U.S.C. §103(a) as being obvious over Weintraub in view of Sharma is overcome. Since claim 2 is not obvious over the reference combination, then dependent claim 6 is also not obvious, since that claim necessarily includes each limitation of base claim 2, from which it depends. Applicant respectfully requests reconsideration and a withdrawal of the rejection of claims 2 and 6 under 35 U.S.C. §103(a) as being obvious over Weintraub in view of Sharma.

CONCLUSION

It is believed that the present Amendment involves the introduction of no new matter and represents a complete response to the Office Action dated October 22, 2010. Applicant therefore

respectfully requests entry of the present Amendment, reconsideration, withdrawal of the rejections under 35 U.S.C. §§102 and 103, and an early allowance of claims 2, 4-7, and 30-33.

It is believed that no additional fees are required, but in the event this is incorrect, please charge any additional fees required in connection with the present Amendment to Deposit Account No. 04-1133.

Respectfully submitted,

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